IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Wouter E. Roorda et al.

Examiner: Carlos A. Azpuru

Serial No.: 10/693,047

Art Unit: 1615

Filed: October 24, 2003

Title: PERMEABILIZING REAGENTS TO INCREASE DRUG DELIVERY AND A METHOD OF LOCAL DELIVERY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR § 1.131

I, Wouter E. Roorda, declare as follows:

1. I conceived of or invented the subject matter of at least independent Claims 12 and 19 as originally filed in the application identified above. I conceived of or invented such subject matter prior to June 8, 2000.

2. I have attached a redacted copy of an invention disclosure form showing the subject matter of the invention as embodied by at least Claims 12 and 19. As can be seen, this selection of pages shows conception of the subject matter of Claims 12 and 19 prior to June 8, 2000.

3. The subject matter of the invention was reduced to practice in a diligent manner, as at least shown by the constructive reduction to practice of the invention merely seventeen (17) months after the filing date of the Walsh reference (U.S. Patent No. 6,689,807). In particular, the filing date of the Walsh reference was June 8, 2000, while the filing date of the parent for the current application was November 30, 2001.

4. I further declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed at Santa Clara, California on this _____ day of October __, 2004.

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By:_____
Wouter E. Roorda
Employee of
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Appendix

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REDACTED

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ADVANCED CARDIOVASCULAR SYSTEMS, INC.

REDACTED

INVENTION DISCLOSURE FORM

REDACTED

1. DESCRIPTIVE TITLE OF THE INVENTION

Use of permeation enhancers in local intravascular drug delivery

2. DESCRIPTION AND USE -

REDACTED

The local uptake of drugs after localized delivery in the vasculature tends to be very low. Part of the reason for this is the limited permeability of the vessel wall. In general, drugs absorbed in the wall of a blood vessel pass through cells and cell membranes rather that between cells. An exception are capillary vessels, which tend to have open pores between their endothelial cells. Therefore, creating channels between cells, or increasing the permeability of cell membranes may lead to increased uptake of drugs that have been delivered to the lumen of the vessel.

Opening channels between cells may be possible by osmotically shocking the tissue.This method has been applied with some success in capillaries of the brain, where tight junctions between cells

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provide a barrier known as the blood-brain barrier. In the application described in this disclosure the osmotic agent, e.g. a sugar solution, can be delivered together with, or just before administration of the drug. The effect of the hyperosmotic sugar solution is to rapidly, but transiently dehydrate cells at the surface of the vessel. This leads to temporary shrinkage of the cells, and exposes underlying tissue to the drug solution.

Alternatively, Ca-ion chelating compounds have been used to open up tight junctions between cells, and may be used to increase the permeability of the endothelial lining of blood vessels. Other compounds, like sodium salicilate and taurodihydrofusidate may serve the same purpose.

Another method is to use surfactant-like molecules that insert themselves into cell membranes and effectively disrupt the dense structure of these membranes. The greater fluidity of the membranes allows for a more rapid permeation of drug molecules, and enhances their uptake into the cells. This type of compounds includes many non-ionic surfactants, like partially hydrolyzed triglycerides, fatty-acid sugar derivatives, oleic acid derivatives etc.

Finally Receptor Mediated Permeation enhancers may be used. This is another approach that has worked to some extent in efforts to pass the blood-brain barrier. These peptide-like molecules activate certain receptor mediated absorption mechanisms. Examples are bradykinin and some of its derivatives.

This disclosure describes methods to improve the local absorption of drugs after intravascular delivery by using of compounds that increase the permeability of the tissue lining the inner wall of a blood vessel.

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This invention can potentially be used in conjunction with any type of local intravascular drug delivery.

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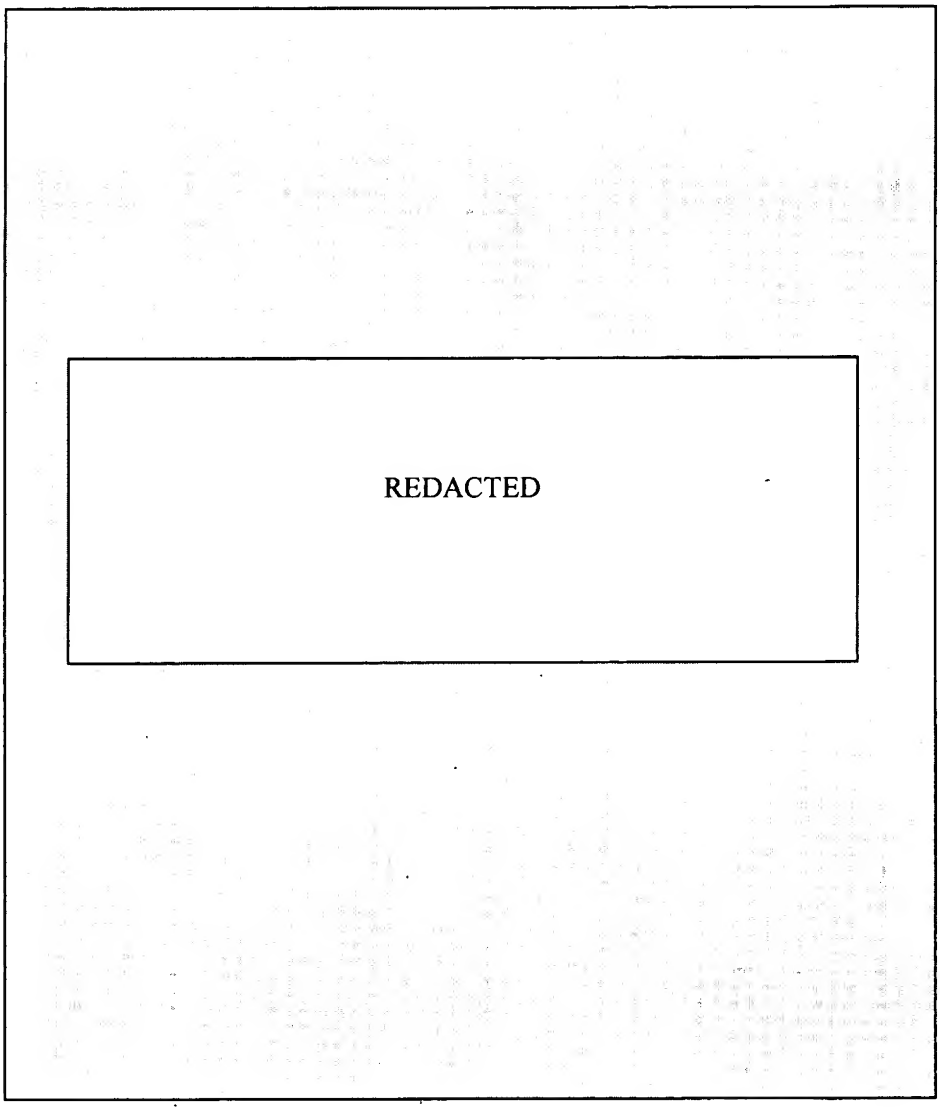

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REDACTED

Read and Understood the completed Invention Disclosure Form (not a Submitter)

REDACTED

10/3/99
Date

REDACTED